Probiotic interventions and quality of life in patients with gastrointestinal diseases: A comprehensive review

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Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2025;34(4):641–658

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Funding sources
None declared

Conflict of interest
None declared

Received on November 20, 2023
Reviewed on April 1, 2024
Accepted on April 29, 2024

Published online on October 8, 2024

Abstract

Gastrointestinal disorders manifest through disruptions in gastrointestinal functionality accompanied by dysbiosis within the microbiome. Probiotics are considered biological agents with potential therapeutic efficacy in managing gastrointestinal pathologies by modulating the gut microbiota. Nevertheless, several hurdles, such as safety considerations, resilience to stressors, post-colonization quantifications, and evaluative modalities, may impede the adoption of probiotics for gastrointestinal disorders. Herein, we performed online research using 6 databases: Scopus, ScienceDirect, PubMed, Web of Science, Cochrane Library, and Ovid. Inclusion criteria were mostly articles published in the years 2015–2024, concerning the association between probiotics and gastrointestinal diseases. This review aimed to provide comprehensive data regarding the latest studies in this area. Additionally, this review delineates the various aspects of probiotic use, including both the positive and negative aspects, as well as the role of probiotics in immune system modulation and the prevention of various diseases. Also, we comprehensively discuss the prophylactic and supportive therapeutic role of probiotics in the management of COVID-19. Given the extensive adoption of probiotic formulations as microecological interventions for gastrointestinal disorders, a comprehensive understanding of the challenges inherent in their application and the implementation of contemporary methodologies to enhance probiotic colonization and evaluation systems are paramount for harnessing probiotics as viable biotherapeutic agents. However, there is a need for additional studies to confirm the potential role of probiotics as a suitable target in the treatment of gastrointestinal diseases.

Key words: microbiome, probiotics, gastrointestinal diseases

Cite as
Qiao X, Zhang H, Shan L. Probiotic interventions and quality of life in patients with gastrointestinal diseases: A comprehensive review. *Adv Clin Exp Med*. 2025;34(4):641–658. doi:10.17219/acem/188108

DOI
10.17219/acem/188108

Introduction

Probiotics, originating from the Greek term signifying "for life", are defined by the Food and Agricultural Organization (FAO) and the World Health Organization (WHO) as "living microorganisms that, when administered in adequate quantities, confer a health advantage to the host".[1] A substantial body of evidence from human observational studies and animal models strongly suggests the involvement of gut microbiota in various chronic human conditions, including gastrointestinal (GI) disorders, cancers, and diseases characterized by inflammatory, metabolic, cardiovascular, autoimmune, neurological, and psychiatric components, hinting at a potential pathogenic correlation.[2,3] Given that the GI tract harbors most microbial cells in the human body, numbering in trillions, alterations in gut flora have emerged as a key mechanism in specific GI disorders.[4,5] Probiotics are pivotal in providing substantial support against the incidence of GI diseases, such as inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS), acute infectious diarrhea, antibiotic-associated diarrhea (AAD), necrotizing enterocolitis (NEC), etc. As research progressed, a paradigm emphasizing bacteria emerged, prompting a reassessment of treatment strategies for GI diseases.[6] Probiotic microorganisms operate through diverse mechanisms, including immune reaction modulation, production of organic acids and antimicrobial agents, interaction with existing microbiota, engagement with the host, fortification of gut barrier integrity, and enzyme generation.[7,8] This review delineates the positive and negative impacts of probiotics, their mechanisms of effect, and their influence on various GI conditions.

Objectives

The objective of this review was to substantiate the hypothesis of using probiotics as an intervention for GI diseases while providing an exhaustive compilation of contemporary research endeavors in this field.

Materials and methods

The review encompassed the utilization of 6 online databases, namely Scopus, ScienceDirect, PubMed, Web of Science, Cochrane Library, and Ovid. Most of the selected articles were published between 2015 and 2024, and focus on the role of probiotics in the prevention and treatment of GI diseases, along with their impact on the quality of life of patients. Original research articles were mostly included, resulting in the incorporation of 24 articles meeting the stipulated inclusion criteria. The data were independently cross-verified by 2 authors. The selection procedure involved the elimination of duplicate entries and subsequent screening based on the title, abstract and full-text review, adhering to the guidelines. Furthermore, an extensive examination of the references cited in the retrieved articles and meta-analyses was conducted to identify additional relevant studies not initially captured in the primary search. The detailed selection process is delineated in Fig. 1.

Results

Regarding the preventative role of probiotics in GI diseases, they exert multifaceted effects. Probiotics demonstrate potential in inhibiting the adhesion of pathogenic bacteria, enhancing barrier functions and interacting with toll-like receptors (TLRs) present on intestinal epithelial cells and dendritic cells (DCs), thereby eliciting cytokines/chemokines to modulate T cell responses. Furthermore, probiotics generate bioactive metabolites that impact the nervous system, consequently influencing gut motility, reducing pain and participating in gut–brain interactions. Notably, probiotics possess the capability to ferment specific types of fiber, leading to increased production of short-chain fatty acids (SCFAs) like propionate, acetic acid and butyrate. Of particular significance, butyrate serves as a pivotal inflammatory modulator, exhibiting anti-inflammatory effects on intestinal epithelial cells, macrophages and leukocytes. Originating from the colonic lumen, butyrate serves as the primary energy source for colonocytes, thereby contributing to the maintenance of the epithelial barrier.[9] Additionally, butyrate intervenes in inflammatory signaling pathways, regulating cytokine production, inhibiting histone deacetylase activity to modulate the expression of proinflammatory genes, and promoting the differentiation and expansion of regulatory T cells (Tregs). Noteworthy research findings indicate that treatment with a probiotic strain of Lactobacillus reduces inflammation and enhances organ survival in specific pathogen-free (SPF) mice. Moreover, probiotic mixtures have been shown to elevate mucin protein secretion and gene expression in the colons of rat.[10]

Definition of probiotics

Probiotics encompass microorganisms, primarily bacteria resembling the beneficial flora naturally found in the human intestinal tract.[11] When provided in sufficient quantities, they bestow a health advantage upon the host.[12] Nevertheless, deceased bacteria and their constituents may also demonstrate probiotic characteristics.[13] They are obtainable without a prescription as over-the-counter (OTC) remedies or through prescribed means, and are accessible in diverse formulations such as capsules, packets or dietary supplements. While many probiotics do not require a prescription, individuals with prescription drug coverage might find an advantage, as probiotics

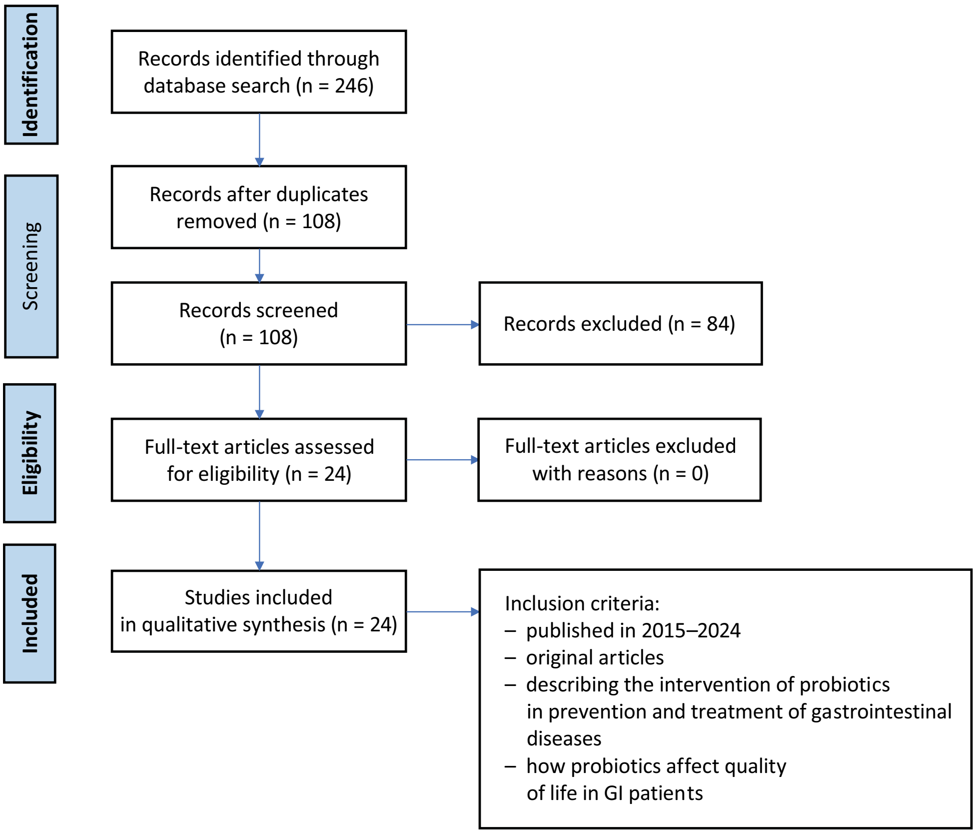

Fig. 1. Study selection process

could be covered under their plan. Extensive research has been conducted on probiotics for various GI disorders, with 1 in 5 Americans using probiotics to address digestive issues. Among the extensively studied probiotics used in humans, the prominent strains include Lactobacillus, Bifidobacterium and Saccharomyces species.[11] Moreover, these bacteria, particularly Lactobacillus, are commonly found in nature. Lactobacillus, Bifidobacteria, Lactococcus, and yeasts fall within the category of organisms considered "generally recognized as safe." Nonetheless, there have been a few reported infections, primarily among immunocompromised patients. It is crucial to note that not all probiotics used fall under this safe category. The effectiveness and safety of probiotics need to be scientifically validated, as emphasized in recent research. Certain evidence indicates that probiotics might enhance the integrity of the gut mucosal defense action, especially by influencing intestinal epithelial cells and macrophages.[14] Probiotics like Bifidobacteria or Lactobacillus have beneficial effects against influenza virus infections of the respiratory tract. Probiotics have a therapeutic effect on managing coronavirus disease-19 (COVID-19) by regulating the gut–lung axis and mucosal immune system, which can potentially have antiviral mechanisms. An adequate number of probiotics can stimulate host innate and adaptive immunities. Interestingly, intestinal bacteria can also have beneficial effects by modulating the vitamin D axis. By doing so, probiotics can protect the mucosal barrier and suppress gut mucosal inflammation.[15,16]

Mechanisms of probiotic actions

The primary function of probiotics lies in their barrier effect, which is intricately linked to the regulation of the host microbiota. This effect establishes a defiance to colonization by impeding or hindering the presence of pathogenic bacteria. The hindrance impact operates through various mechanisms, including the obstruction of bacterial attachments and the rivalry for attachment locations. Additionally, probiotics operate as secondary agents by improving the protective capability of the intestinal lining, which relies on the tight connections between intestinal epithelial cells. They also contribute to this function by producing mucus containing antimicrobial peptides like defensins and lysozyme, as well as Paneth cells. This mucus layer acts as a shield, averting direct contact between the digestive channel and bacteria. Probiotics operate through a third mechanism, exerting an influence on the immune system. It is crucial to emphasize that over 70% of immune cells reside within the gut-associated lymphoid tissues, which are predominantly concentrated in the small intestine. Certain probiotic bacteria, notably lactobacilli, can induce either localized or systemic effects depending on their cytokine profile. It is imperative to thoroughly comprehend the mechanisms through which probiotics operate. Moreover, the properties of probiotic strains must remain unchanged throughout the production process and storage period before their use, ensuring the absence of any factors that may cause diseases.[17]

Each probiotic strain exerts a distinct effect, making it imperative to conduct individual assessments to determine their specific health benefits. The efficacy remains unproven because of the limitations of existing studies, such as their low quality, variations in microbiota, reactions to attempts at adjustment, and the diverse range of probiotic strains employed.[18]

Risk theories of probiotics usage

Numerous risk theories revolve around probiotics use. One concern involves the possibility that probiotics cause infections via translocation. Certain strains have shown the ability to either decrease or increase the movement of gut bacteria, thereby influencing this process. In addition, probiotics might produce poisonous compounds such as D-lactate during bacterial fermentation that can be a potential risk factor, leading to lactic acidosis. In cases of children with short bowel syndrome, administration of lactobacilli-rich microbiota or specific Lactobacillus probiotic strains has been linked to acidosis, leading to either encephalopathy or hyperventilation. Nevertheless, there have been no reported cases of lactic acidosis in healthy children. Yet another notable risk involves the exchange of antibiotic-resistance genes between typical host bacteria and probiotic strains residing in the digestive tract. This gene transfer can occur within the gut microbiota, potentially increasing bacterial diversity in the area. Probiotic strains can serve as vectors for these resistance genes, acting as either an offeror or applicant. It is recommended to select probiotic strains that do not possess acquired and potentially transferable resistance genes. Concerns arise when using probiotic strains from species that naturally carry virulence and antibiotic resistance traits, such as Enterococci or *Escherichia coli*. Genomic analyses of probiotic enterococci strains indicating the absence of virulence factors can alleviate this concern.[17]

Challenges of probiotic application in the treatment of gastrointestinal diseases

Although probiotics demonstrate considerable potential for the treatment of GI disorders, their implementation is constrained by a number of challenges.[19] First, for probiotics to be deemed safe for human consumption, they must lack transferable antibiotic-resistant genes.[20] Consequently, the use of engineered probiotics in disease management is often restricted. Second, a minimum viable count of approx. 10^6 colony-forming units per gram (CFU/g) is necessary for probiotics to exert their beneficial effects.[21] However, widely used probiotics such as Lactobacillus and Bifidobacterium are highly vulnerable to aerobic and high-temperature conditions. The next generation of probiotics requires an environment conducive to their viability and robustness to endure the acidic stomach and bile environment during their transit through the GI tract. Even upon successful passage to the colon without damage, probiotics must adhere to the mucosal layer and establish effective colonization to be efficacious. Thus, formulating probiotics for targeted delivery to the intestines poses significant challenges. Bacteriocins serve as versatile agents, functioning as "colonizing peptides", "killing peptides" and "signal peptides", augmenting the colonizing potential of the producing strain in the gut and providing it a competitive edge over other strains. In addition, unresolved issues persist regarding probiotic quantification, encompassing on-site localization and dynamic monitoring.[22] Moreover, the gut microbiota substantially influences the development and functioning of the immune system, among other physiological processes. The symbiotic relationship between the gut microbiota and the host organism offers numerous mutual benefits, as the microbiota within the host organism performs crucial functions (Fig. 2).

Positive aspects of probiotics usage

Metabolism, the barrier effect and trophic functions, recognized as pivotal aspects of intestinal physiology, constitute the primary roles of the microbiota.[18] Dysbiosis, denoting bacterial imbalance, can lead to various diseases. It is widely known that the introduction of live bacteria (probiotics) or indigestible substrates (prebiotics) leads to a positive response from the microbiota, helping to prevent and even treat specific diseases. Presently, there is a widespread acknowledgment of the substantial impact of intestinal microbiota on human health, and probiotic interventions are recognized as a means to modulate this influence.[17] According to the guidelines established by the WHO and the FAO, a bacterial strain can be classified as a probiotic only if it effectively reaches the targeted site in the body and withstands physiological stressors such as the acidic environment, varying pH levels in the stomach and intestines, and bile salts. Furthermore, a probiotic should demonstrate established beneficial effects on the host, be devoid of risks, and maintain its properties during both production and storage. Probiotic microorganisms can originate from diverse genera and species,[23] including yeasts like *Saccharomyces cerevisiae* and bacteria such as Lactobacillus, Streptococcus, Enterococcus, Bifidobacterium, Propionibacterium, Bacillus, and *E. coli*. These probiotics can either naturally exist in commonly consumed foods or be genetically modified for specific purposes. Notably, strains from the Enterococcus genus carry a heightened risk potential compared to other probiotics; although infrequent, they may cause systemic infections and antibiotic resistance in the host. Probiotic products may contain either a single strain or multiple strains.[24] The advantages of a probiotic formulation vary based on the specific patient demographic. Studies with limited scope have indicated heightened effectiveness

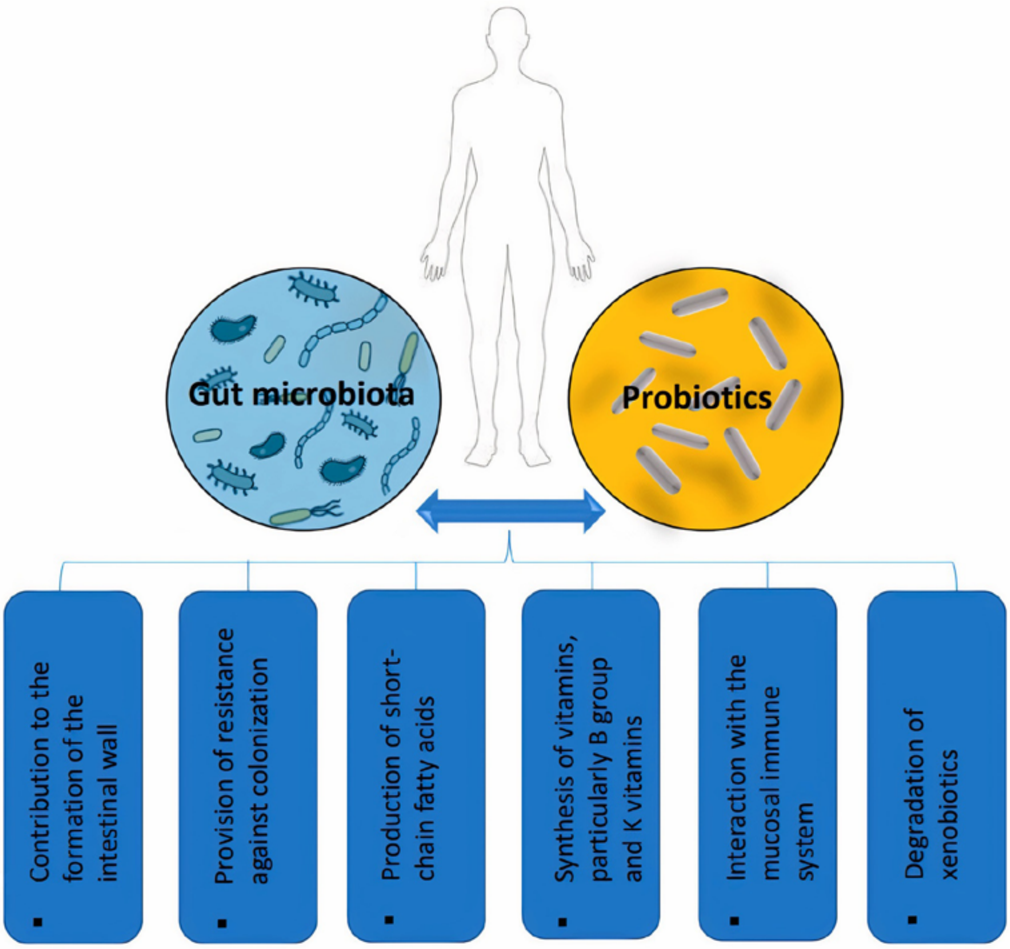

Fig. 2. The relationship between the gut microbiota and the host organism is advantageous

when utilizing probiotics sourced from diverse ethnic backgrounds. To regulate the consideration of probiotics in food, the WHO and the FAO have jointly established comprehensive guidelines. These FAO/WHO guidelines serve as the global standard for probiotic assessment. The prescribed instructions under this directive encompass the following criteria: probiotics offer several key advantages, including safeguarding against GI pathogens, enhancing immune function, reducing serum cholesterol and blood pressure levels, exhibiting anti-carcinogenic properties, and enhancing nutrient utilization and bioavailability.[25] These benefits are achieved through diverse mechanisms, including a decrease in intestinal pH, inhibition of pathogenic organism colonization and invasion, and modulation of the host immune response.[26]

Probiotics' role in immune system modulation

The gut microbiota plays a pivotal role in immune system regulation through the production of molecules possessing immunomodulatory and anti-inflammatory properties. These effects result from the interactions between probiotic bacteria and various cell types, including epithelial cells, DCs, monocytes/macrophages, and lymphocytes, thereby initiating and stimulating immune cell activity.[27] Probiotics fundamentally contribute to regulating the host immune response, which is categorized into innate and adaptive systems. The adaptive response involves the specific binding of B and T lymphocytes to antigens, while the innate system recognizes common structures known as pathogen-associated molecular patterns (PAMPs) shared by numerous pathogens. Pattern recognition receptors (PRRs) bind to PAMPs, triggering an initial response to pathogens. These PRRs encompass a diverse array of molecules, including transmembrane proteins like TLRs, found in various immune and non-immune cells such as B cells, natural killer cells, DCs, macrophages, fibroblast cells, epithelial cells, and endothelial cells. Additionally, PRRs encompass nucleotide-binding oligomerization domain-like receptors (NODLRs) that safeguard the cytoplasmic space. Other recognized PRRs include C-type lectin receptors, formylated peptide receptors, retinoic acid-inducible helicases, and intracellular IL-1-converting enzyme protease-activating factor.[28] Notably, the finely tuned regulation of the T cell subset, which is crucial for maintaining immune balance, is influenced by both the host and interacting microbes. Imbalances between effector T-helper (Th) cells and Tregs can compromise immune responses. Probiotics aid in preserving intestinal equilibrium by modulating the immune response and promoting Treg proliferation.[13]

Prebiotics

Prebiotics possess distinctive attributes: First, they resist enzymatic breakdown in the human gut and are specifically metabolized by certain genera/species of resident gut microbiota. This targeted breakdown leads to an increase in particular bacteria, providing health advantages to the host. These benefits encompass various effects, such as immune modulation characterized by elevated levels of intestinal-specific immunoglobulins and immunoregulatory interleukins, alongside a decrease in proinflammatory interleukins. In addition, prebiotics induce the production of SCFAs like acetate, propionate, butyrate, and lactate, thereby reducing the gut's pH level. This pH adjustment is crucial to preventing the colonization of acid-sensitive enteric pathogens. Notably, acetate production contributes to the synthesis of butyrate through cross-feeding, acting as a fundamental element for colonocyte function and enhancing epithelial integrity.[29,30] Although dietary fiber found in fruits and vegetables is generally indigestible, not all varieties exhibit prebiotic effects. Certain vegetables like leeks, asparagus, chicory, garlic, and artichoke, as well as grains such as wheat, and fruits like bananas, oats and soybeans, contain compounds such as inulin, fructo-oligosaccharides and galacto-oligosaccharides (GOS). These substances serve as major prebiotic substrates. Research suggests their potential to stimulate the growth of specific colonic microbiota, potentially offering health benefits to the host.[29] Typically, prebiotics include dietary carbohydrates, predominantly featuring inulin-type fructans and GOS as the primary types meeting prebiotic criteria, although ongoing research explores various other carbohydrate classes in this domain.[29,30]

Bacteriocins and other bacterial antimicrobial compounds

Numerous intestinal bacteria create antimicrobial peptides, proteins and lipoproteins to improve their dominance in particular anatomical locations. Bacteriocins, with their limited range, excel at eradicating bacteria in close proximity to the producing strain, ensuring steady colonization and thwarting intrusion from rival species. For example, *Enterococcus faecalis* strains that generate new bacteriocins can surpass strains that do not produce them. The genetic material responsible for these bacteriocins can be transferred horizontally, hinting at the possible usefulness of introducing bacteriocin-producing strains to decrease the presence of multidrug-resistant enterococci.[31,32] Many research studies have highlighted the importance of probiotic microbes that produce bacteriocins in safeguarding food safety and packaging, especially in the fight against Gram-positive bacteria such as Listeria.[33] The identified bacteriocins are systematically categorized based on their design and antimicrobial spectrum in databases such as BAGEL[34] and BACTIBASE[35] and are extensively discussed in recent reviews.[36–38] Bacteriocins can have effects beyond direct antimicrobial activity. For instance, mice fed a high-fat diet did not experience changes in the composition of their intestinal microbiota when given *Lactobacillus plantarum* strain NCMIB8826, which produces the bacteriocin plantaricin EF. However, compared to mice fed a mutant *L. plantarum* strain lacking bacteriocin, zonulin expression increased. In vitro studies further confirmed a reduced permeability upon exposure to bacteriocin. Ongoing research is currently focused on this area[39] in case bacteriocins can translocate into the lamina propria and initiate systemic effects.[40]

Probiotics in the prevention or treatment of different disorders

Inflammatory bowel diseases

In recent decades, there has been a noticeable upward trend in the global incidence and prevalence of inflammatory bowel diseases (IBD). Ulcerative colitis (UC) and Crohn's disease (CD) stand out as the 2 primary subtypes of IBD, with UC predominantly affecting the large bowel, and CD manifesting in any part of the GI tract. The exact etiology of UC remains a subject of substantial debate, with proposed factors including environmental influences, immune dysfunction and genetic predisposition.[41] The prevailing hypothesis suggests that genetically susceptible individuals harbor abnormalities in humoral and cell-mediated immunity, leading to heightened reactivity against commensal intestinal bacteria, thereby predisposing them to colonic inflammation. The causal relationship between these abnormalities and the intense systemic inflammatory response observed in UC remains unresolved. Nevertheless, it is well-documented that patients with active UC exhibit alterations in bacterial microflora. Recent studies have highlighted considerable variability in the effects of the microbiota, particularly emphasizing the influence of a proinflammatory enterotype on mucosal integrity and disease activity.[42] While modulation of the intestinal microbiota can be achieved through antibiotics or probiotics, antibiotic use for chronic diseases should be limited due to concerns regarding resistance, potential side effects and ecological impacts. Therefore, the use of probiotics in IBD management holds promise as a potential adjunct to current conventional therapies. A comprehensive analysis of scientific data attests to the demonstrated and confirmed efficacy of probiotics in treating various diseases. Several studies have particularly focused on the effects of probiotic blends on the enteral microbiota, particularly in cases of dysbiosis, wherein the normal concentration of beneficial bacterial flora is compromised by the presence of pathogenic bacteria.[43]

Irritable bowel syndrome

Functional GI disorders, including ailments such as abdominal pain and irritable bowel syndrome (IBS), constitute common reasons for pediatric gastroenterologist consultations. These conditions are prevalent among school-aged children, affecting approx. 10% of this demographic, with potential regional discrepancies. For instance, IBS has been reported in 13% of children in China, 10% in the USA and 6% in Sri Lanka.[44] In contrast, IBS in adults exhibits varying prevalence rates, ranging from 6% in Africa and the Middle East to 18% in Latin America.[45] The prevalence in North America and Asia typically falls between 8% and 10%. The multifaceted etiology of IBS includes factors such as genetic predisposition, responses to life stresses and potential environmental triggers like infectious diarrhea. The Rome Criteria provides a precise definition, defining IBS as recurrent abdominal pain occurring at least once a week for over 3 months, accompanied by changes in bowel movements and stool form and/or frequency. Recent studies have highlighted an altered microbial composition in the feces of individuals with IBS. Particularly, those with diarrhea-predominant IBS exhibit a distinct microbial profile, characterized by reduced microbial diversity, diminished populations of butyrate-producing organisms (crucial for gut barrier function) and fewer methane producers (involved in gas expulsion).[46] These findings emphasize the potential role of targeted microbial interventions in managing IBS. Probiotics have been extensively investigated in numerous randomized controlled trials (RCTs) to assess their effectiveness in alleviating IBS symptoms. Ford et al.[47] conducted a comprehensive analysis encompassing 43 RCTs involving over 3,000 participants, revealing a relative risk (RR) of persistent IBS symptoms at 0.79 (95% confidence interval (95% CI): 0.70–0.89) in favor of probiotic use. Additionally, a recent review of 21 RCTs in China showcased a positive association between probiotic consumption and improved IBS symptoms, coupled with an enhancement in quality of life.[48] However, these studies presented differing conclusions. One study indicated superior outcomes with a single probiotic, while the other found similar results with both single and multi-organism probiotics. Recent RCTs have meticulously examined individual probiotics, facilitating meta-analyses that highlighted their effectiveness in individuals with IBS. Noteworthy probiotics in these analyses include *S. cerevisiae* CNCM I-385620 and *Bifidobacterium infantis* 35624.[49] The latter demonstrated efficacy specifically when incorporated into a multi-organism probiotic. Essentially, individuals with IBS exhibited a reduction in specific symptoms like flatulence, abdominal pain and constipation in response to probiotics, while discernible changes were not evident in other symptoms such as bloating or urgency. Furthermore, *Lactobacillus reuteri* showed beneficial effects in children with functional abdominal pain, leading to a decrease in episode frequencies and pain intensity.[50] Although probiotics offer advantages for children with IBS, their impact appears relatively modest compared to alternative treatments like low-dose antidepressants.[51] Several key questions persist, including the magnitude of the effect, optimal dosage, safety in vulnerable populations, and identification of the most effective probiotic species and strains.

Acute infectious diarrhea

Acute diarrhea, often caused by viruses, primarily affects children aged 6 months to 2 years. Its occurrence is closely related to water quality, sanitation and hygiene. Infants with acute diarrhea are at high risk of dehydration, a leading cause of child mortality globally, causing about 700,000 deaths annually.[52] Probiotics, particularly *Lactobacillus rhamnosus* GG and *L. reuteri*, have been extensively studied for over 3 decades in treating acute diarrhea in children. Parker et al.[53] reviewed 15 studies on *L. rhamnosus* GG, finding it reduces the severity and duration of diarrhea, most effectively at doses of 10^{10} CFU. Their meta-analysis also showed that *L. reuteri*, at a lower dose, effectively shortens diarrhea duration by about 1 day.[54] Global efforts in hygiene, breastfeeding and rotavirus vaccination have decreased diarrhea-related deaths; however, recent refugee crises may challenge this progress. The broader effects of such measures remain a subject of interest.

Antibiotic-associated diarrhea

Antibiotics are frequently prescribed for children, with over half of those under 18 receiving at least 1 course, including commonly prescribed types like amoxicillin, azithromycin and amoxicillin/clavulanate. Antibiotic-associated diarrhea (AAD) affects approx. 11% of all children receiving antibiotics and reaches 18% among those under 2 years of age.[55] Hempel et al. conducted a meta-analysis involving 63 RCTs and 11,811 subjects, predominantly using Lactobacillus as the probiotic. Their findings showed a reduced risk of AAD (RR: 0.58; 95% CI: 0.50–0.68; $p < 0.001$) in individuals using probiotics. However, there was some variability in outcomes, prompting further investigation to determine the most effective probiotic regimen. A recent meta-analysis in China, encompassing 30 trials and over 7,000 participants, predominantly focusing on children and consistently containing Bifidobacteria strains in the probiotic, revealed a significant efficacy in preventing AAD, with an odds ratio (OR) of 0.34 (95% CI: 0.23–0.43; $p < 0.01$) for AAD occurrence among children administered Bifidobacteria-containing preparations, highlighting the clinical importance of such interventions.[55]

Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) poses a significant risk to premature infants, affecting 5–10% of those born weighing 500–1500 g. Nearly half of these infants require surgical intervention, with mortality rates ranging between 20% and 30%. Necrotizing enterocolitis is the primary cause of short bowel syndrome in children.[56] In a 4-year multicenter trial, Warner et al. investigated the progression of microbial colonization in preterm infants and noticed disruptions occurring before NEC onset. They observed an expansion of Negativicutes in non-NEC cases. However, infants diagnosed with NEC displayed reduced Negativicutes and increased Gammaproteobacteria strains, indicating a correlation with GI dysbiosis.[57] Multiple meta-analyses corroborate the effectiveness of probiotics in preventing NEC.[58] However, determining the most effective probiotic strain remains unknown due to the variations in preparations used across studies. No studies on probiotics in preventing NEC have been completed in the USA. Safety concerns persist, with the U.S. Food and Drug Administration (FDA) categorizing probiotics similarly to vaccines. Essential preclinical and clinical trials are required to understand early-life host–bacterial interactions. Studying the immune response and microbiota impact in infants solely fed with breast milk, especially involving strains like *L. rhamnosus* GG and *L. reuteri*, holds potential. However, it is essential to exercise caution and avoid exceeding doses of 10^{10} CFU in premature neonates to mitigate the risk of bacterial translocation. Despite these safety considerations, probiotics, particularly in very low birth weight (VLBW) infants (<1,000 g), are anticipated to offer substantial preventive advantages against NEC. An initiative that introduced *L. reuteri* probiotics showcased a significant 6-fold decrease in the risk of NEC after implementation.[58]

Infant colic

Colic, characterized by excessive crying and fussiness in infants, typically emerges between 3 weeks and 3 months of age, affecting up to 10% of infants. It has been associated with potential cases of child abuse and infanticide, often arising from a caregiver's attempts to alleviate the distressing crying episodes.[59] Various theories have been proposed to elucidate the origin of colic, including parental stresses, cow milk protein allergies, the 4th-trimester theory, and the inflammation-dysbiosis theory. While these theories offer insights into specific cases, dysbiosis (an imbalance in gut microbiota) and gut inflammation consistently emerge as noteworthy factors.[60,61] Research conducted in different regions has identified alterations in the microbial composition of infants with colic. These include increased *E. coli*, reduced Lactobacilli, elevated Klebsiella, and a diminished microbial diversity.[60,61] These findings suggest a potential link between gut microbiota and colic. Studies investigating the probiotic *L. reuteri* have shown promising results. Administered as liquid drops in sunflower oil, it demonstrated notable benefits in breast-fed infants with colic, reducing crying and fussy times. However, its effectiveness in formula-fed infants remains a subject of debate, possibly due to various factors, including differences in probiotic strains and sample sizes.[62,63] Presently, colic is often treated with acid blockers, despite their efficacy being limited, and their potential drawbacks. The introduction of a safe and effective treatment option like *L. reuteri* represents a significant advancement in pediatric care.[64] The positive effects of probiotics on infants are mentioned in Fig. 3.

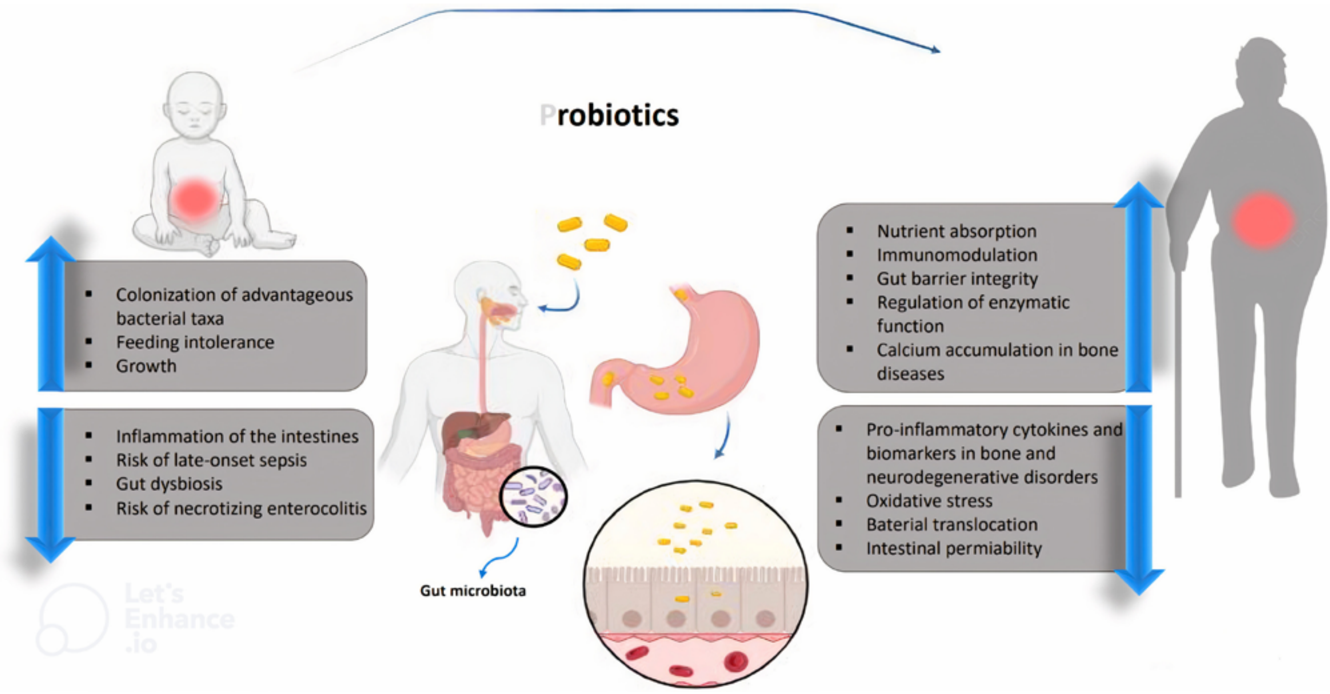

Fig. 3. The role of probiotics in infants and the elderly

Upper respiratory infections

In studies conducted at daycare centers, regular probiotic intake among healthy children demonstrated a nearly 25% decrease in absent school days.[65] Probiotics exhibit a consistent impact by promoting an immune response, resulting in heightened production of immunoglobulin A (IgA)-secreting cells in both the respiratory and GI mucosa.[66] Moreover, comprehensive analyses have affirmed the correlation between probiotics and diminished severity of symptoms, along with a shorter duration of respiratory tract infections, typically by approx. 1 day.[67]

Allergic diseases

Balancing a dual role of defending against emerging organisms while tolerating nonpathogenic antigens/allergens, the immune system's primary mission is to safeguard the host. This undertaking is formidable, necessitating alliances in an ongoing battle.[68] Probiotics have emerged as a clear ally in regulating the interplay between inflammation and allergic responses. The hygiene hypothesis, supported by epidemiological data, suggests a reduced susceptibility to allergic diseases among individuals in rural and developing regions. This interest in probiotics for preventing or managing allergic conditions like asthma, eczema and food allergies has grown significantly.

However, meta-analyses revealed that probiotics may not be sufficient to prevent asthma, allergic rhinitis or food allergy onset, except for atopic dermatitis. The impact of probiotics on atopic dermatitis varies and lacks consistent demonstration across studies.[69] A recent meta-analysis involving 17 studies shows a noteworthy reduction in eczema risk for infants when both mothers and infants receive probiotic supplementation, especially a mixture of probiotics. Probiotics hold an intriguing potential as adjuncts in oral immunotherapy (OIT) for food allergies. In a recent double-blind, placebo-controlled trial, administering the probiotic *L. rhamnosus* CG MCC 1.3724 alongside peanut OIT resulted in sustained unresponsiveness in 82% of children with peanut allergies, compared to only 3.6% in the placebo group.[70] Unfortunately, despite this success, probiotics have not shown significant therapeutic efficacy in treating allergic rhinitis and asthma in RCTs.[71] While ongoing clinical trial data suggest some beneficial effects of probiotics in preventing and managing allergic diseases, the evidence is not strong enough yet to support a universal recommendation for their therapeutic use. Various factors, including the specific probiotic strains tested, as well as patient-specific factors such as diet, immune responses, mucosal conditions, and emotional states, can influence probiotic functionality. Additionally, the route of administration could play a crucial role; for instance, nasal spray delivery may be more effective for allergic rhinitis, inhalation for asthma, and topical application for atopic dermatitis. Further research is imperative, particularly in unraveling the diverse mechanisms through which probiotics contribute to immunoregulation and mucosal homeostasis.

Clostridium difficile colitis infections in hospitalized patients

Clostridium difficile colitis arises as an opportunistic infection due to disruptions in the normal gut flora induced by antibiotic administration. Antibiotics such as clindamycin, fluoroquinolones, broad-spectrum penicillin, and cephalosporin are commonly associated with this condition. The severity of *C. difficile* colitis varies, with severe cases necessitating intensive care and posing a lethal risk. Probiotics are nonpathogenic bacteria that reside in the GI system and produce lytic peptides that impede the activity of *C. difficile* toxins. Specifically, *Saccharomyces boulardii* generates a protease that inhibits the action of *C. difficile* toxins.[72]

Prophylactic probiotics aim to establish the presence of beneficial bacteria to combat *C. difficile* overgrowth. Certain probiotics demonstrate the capacity to neutralize *C. difficile* toxins A and B, as supported by in vitro and preclinical data, conferring protective properties.[73] Postoperative patients are vulnerable to bacterial translocation, primarily stemming from intestinal mucosal injury, leading to gut barrier disruption, heightened intestinal permeability, microbial imbalance, and diminished immunodeficiency. This risk is particularly pertinent in abdominal surgeries for conditions like biliary cancer, pancreaticoduodenectomy and liver transplantation, predisposing patients to complications such as urinary tract infection (UTI), pneumonia, wound infection, intra-abdominal abscess, and cholangitis.[74,75]

Administering probiotics alongside antibiotics in adult non-surgical infection patients has shown promise in reducing rates of *C. difficile* colitis. This approach holds potential for infection prevention, potentially leading to decreased morbidity, shorter antibiotic therapy durations, reduced hospital stays, and a mitigated risk in the emergence of antimicrobial resistance.[75,76]

Probiotics in very low birth weight infants

Newborns with VLBW experience considerable neonatal morbidity and mortality, primarily linked to nosocomial infections and NEC. The multifaceted origins of these conditions involve intrinsic host factors like gestational age and underdeveloped immune responses. Moreover, environmental aspects such as enteral nutrition and exposure to a hospital environment harboring pathogen significantly influence the abnormal colonization of the GI tract and the movement of pathogenic bacteria across the fragile intestinal lining.[77,78]

The use of *Lactobacillus acidophilus/Bifidobacterium infantis* probiotics has shown a noteworthy correlation in the prevention of NEC surgery and any abdominal surgery, accompanied by a decrease in overall mortality. This hints at a potential mechanism by which probiotics may enact their effects, involving a mutual interplay between the evolving immune system and gut microbiota.[79]

Prophylactic intervention involving probiotics in the context of cancer (carcinogenesis)

Colorectal cancer patients exhibit distinct gut bacteria profiles. Bacteroides and Prevotella are more prevalent, while colorectal adenoma patients have higher levels of *Dorea* spp. and fecal bacteria spp. These bacteria can produce compounds linked to carcinogenesis and tumor promotion.[80]

Probiotics not only defend against infections but also possess potential anticancer properties. They play a vital role in immunomodulation and have been shown to mediate anticancer responses. Specific strains may be involved in the detection and breakdown of potential carcinogens. They also contribute to the synthesis of SCFAs, crucial for regulating cell proliferation and apoptosis. Additionally, heat-killed probiotic bacteria combined with radiation have shown promise in enhancing cancer cell immunological recognition.[81]

A combination of *Lacticaseibacillus rhamnosus* GG, *Bifidobacterium lactis* Bb12 and oligofructose-enriched inulin administered to colorectal cancer patients resulted in beneficial shifts in the gut microbiome. This intervention led to increased levels of advantageous bacteria and decreased levels of detrimental bacteria. *Lacticaseibacilli casei* has displayed augmented immune responses against cancer and alleviation of side effects from cancer treatments.[13] Nevertheless, further investigation is necessary to comprehend the precise mechanisms underlying probiotic-induced anticancer effects.[82] Potential pathways may involve the interplay between nutrition, gut microbiota and host energy metabolism, yielding diverse effects.[83] These effects encompass neutralizing carcinogens, fortifying intestinal barrier functions, synthesizing essential compounds, modulating immune responses, and influencing apoptosis, among other factors.[84] Exposure to Lactobacillus induces various biological changes, including increased levels of cytokines, interleukins, antioxidants, microbial flora, interferons, and immune cells, while simultaneously reducing factors like DNA damage, pathogens, inflammation, ulcers, tumor size, cancer-specific proteins, polyamine contents, and pro-carcinogenic enzymes.[79]

In rat experiments, a combination of probiotics and celecoxib demonstrated a reduction in the expression of the proto-oncogene K-ras and an elevation in the tumor suppressor p53. This suggests a potential synergistic effect inhibiting cell growth by activating tumor suppressor genes while preserving cell activity and the cell cycle. This combined treatment likely contributed to maintaining gut integrity, enhancing the immune response, and leading to reduced DNA damage.[85] Additionally, celecoxib's anti-inflammatory properties contributed to a decrease in colonic tumors by downregulating K-ras and upregulating p53, which can induce Bax-mediated apoptosis.[85,86]

Additionally, DNA methylation, facilitated by differential methylation hybridization (DMH), triggers activation in the Wnt pathway. This pathway's acceleration, attributed to the increased expression of proinflammatory markers, contributes to the process of carcinogenesis. The participation of detrimental bacteria, the production of harmful metabolites, and a decrease in pro-apoptotic markers further exacerbate this progression. By administering probiotics and celecoxib, the modulation of the Wnt signaling pathway occurs along with improvements in the gut microbiome. This intervention potentially leads to decreased inflammation and heightened apoptotic markers, serving as a preventive measure against the onset of carcinogenesis.[85]

Probiotics and enteral nutrition in acute pancreatitis

In cases of acute pancreatitis, a significant aspect of pathogenesis involves bacterial translocation from the stomach to necrotic pancreatic tissue. This process leads to infection of the pancreatic tissue. Preventing bacterial translocation and subsequent infection in cases of pancreatic necrosis is a key concern. To achieve this, prophylactic approaches such as antibiotics, enteral nutrition or probiotics can be used. Studies conducted in mouse models have demonstrated that administering probiotics as a pre-treatment, especially in the early stages, can effectively uphold intestinal barrier function, even in severe pancreatitis. Notably, the timing of probiotic administration plays a critical role in their efficacy. Whereas animal models have provided evidence of a correlation between probiotic timing and pancreatitis onset, it remains to be firmly established in human subjects, warranting further investigation.[87,88]

Late-onset sepsis in preterm infants

Gram-negative bacteria, while less prevalent than their gram-positive counterparts, are linked to late-onset sepsis (LOS), marked by a more severe clinical course, higher mortality rates and increased neonatal morbidity. Late-onset sepsis can be caused by factors such as low birth weight, premature delivery or admission to the intensive care unit (ICU). Premature infants, especially those in the ICU, are susceptible to bacterial colonization. The use of antibiotics after birth and prolonged hospital stays can lead to a decrease in the diversity of microbes in the microbiome.[88] In this vulnerable population susceptible to LOS, the administration of oral probiotics may enhance the colonization of beneficial bacteria. It is important to note that the effectiveness of probiotics depends on factors like the specific strain, dosage and intended use. A recent RCT focused on preterm infants between 28 and 31 weeks of gestation and demonstrated a significant reduction in LOS incidence with a probiotic combination comprising *B. infantis*, *Streptococcus thermophiles* and *B. lactis*.[88]

Necrotizing enterocolitis in preterm infants

Necrotizing enterocolitis is a condition that causes the death of intestinal tissue and is a significant contributor to neonatal mortality, affecting around 20–30% of VLBW infants, defined as those born weighing less than 1,500 g (1.5 kg). Premature neonates frequently encounter delayed and diminished colonization of the gut by probiotic organisms like Bifidobacteria and Lactobacilli. Various factors, including cesarean birth, delayed breastfeeding initiation or antibiotic treatment after birth, can lead to an imbalance favoring potentially harmful bacteria.[89] Enteral administration of probiotics has demonstrated efficacy in preventing severe NEC and reducing overall mortality in preterm infants.[90] The prophylactic use of enteral probiotics, involving the supplementation of live microbial organisms, holds promise in mitigating NEC and its associated morbidity. This is achieved through hindering bacterial migration across the mucosa, competitively excluding harmful bacteria, and enhancing the host's immune responses. Notably, probiotics containing *L. acidophilus* and *B. infantis* have shown associations with a reduced risk of NEC-related surgery, any abdominal surgery and overall mortality.[91]

The mechanism of probiotic action involves facilitating the establishment of beneficial microbial flora in the gut, preventing pathogenic colonization, strengthening the maturity and functionality of the gut mucosal barrier, and influencing the immune system. Typically, probiotics are administered for a duration of 2 weeks, starting either on the 1st day of life for newborns not receiving antibiotics or after the cessation of antibiotic therapy.[91,92]

Ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is a serious risk for patients in ICUs and can cause morbidity and mortality. Probiotics have recently emerged as a promising tool in combating VAP. The proposed mechanisms of probiotics include strengthening the intestinal barrier, increasing the production of antimicrobial peptides in host cells, regulating gut microbiota composition, and curtailing the proliferation and translocation of harmful bacteria. Multiple trials have validated the safety and efficacy of probiotics in both preventing and treating VAP among ICU patients.[93,94]

Probiotics and their therapeutic uses

Probiotics exert their predominant therapeutic effects through their direct or indirect actions on the GI tract. Their efficacy is derived not just from interactions with host cell mucous membranes but also from their oral intake. However, it is crucial to acknowledge that while certain probiotic microorganisms offer advantages, not all are naturally prevalent in the human gut flora. Therefore, the benefits attributed to one species might not universally apply to others[95] (Table 1).[95–123]

In vitro and in vivo models

Bacterial growth inhibition models

There are several GI illnesses caused by common pathogens such as *E. coli*, *C. difficile*, Salmonella, *Helicobacter pylori*, Listeria, and *Candida albicans*. Traditionally, researchers have utilized in vitro methods to evaluate the potential efficacy of probiotics in inhibiting the growth of these pathogens. For example, Prasastha Ram et al. conducted studies showcasing the antibacterial and antibiofilm properties of *L. acidophilus* against multi-drug-resistant *Enteroaggregative Escherichia coli* (MDR-EAEC) strains using green synthesized silver nanoparticles.[124] Ruiz et al. explored a synbiotic containing *Bifidobacterium longum* subsp. *infantis* CECT7210 and oligosaccharides, demonstrating its antimicrobial efficacy against *E. coli*, *Cronobacter sakazakii*, *Listeria monocytogenes*, and *C. difficile*.[125] Similarly, Cizeikiene and Jagelaviciute identified potential probiotic candidates like *L. acidophilus* DSM 20079, *Bifidobacterium pseudolongum* DSM 20099 and *Bifidobacterium animalis* DSM 20105 through antibacterial assays targeting various pathogenic strains.[126] In addition to pathogen growth inhibition, researchers have explored the effects of probiotics on pathogenic and host-related infection genes. *Bifidobacterium longum* JDM301 was found to inhibit *C. difficile* growth and promote clostridial toxin degradation.[127] Ghadimi et al. conducted an assessment of the probiotic effects of *B. animalis* R101-8. They evaluated the expression levels of genes linked to lipid metabolism and cytokines associated with inflammation. Their study suggested that *B. animalis* R101-8 might elevate meta-inflammation biomarkers through molecular pathways activated by proinflammatory bacteria and lipids.[126] Furthermore, the development of mathematical and genome-scale metabolic models in big data science and bioinformatics has resulted in innovative methods for assessing the functions of bacterial probiotics.[128,129]

Models simulating intestinal microbiota in vitro

Recent advancements in batch fermentation techniques, especially those replicating the conditions of the distal colon, provide opportunities for exploring interactions between probiotics and pathogens. Several models, such as TIM-2, SHIME, ECSIM, SIMGI, PolyFermS, and EnteroMix, have been created to mimic the human intestinal microbiota.[130] Although these models were mainly

Table 1. Application of probiotics for therapeutic purposes

Disease	Definition	Etiology	Probiotic strain	Mechanism of action	Useful product	Ref.
IBD, including: (UC and CD)	Persistent inflammation of the gut mucosa. Disruption of gut barrier function/an imbalanced microbiota frequently manifest as chronic gastrointestinal mucosa inflammation.	An issue arises from the immune system's reaction to microorganisms within the natural intestinal flora. Alterations in the gut microbiota or a weakening of the mucosal barrier lead to detrimental immune reactions against the mucosa.	*Lactobacilus paracasei* L74 CBA/ *Streptococcus salivarius/ Lactobacilus salvarius/ Lactiplantibacillus plantarum* Lp91	Anti-inflammatory effect. Reduction in the levels of (COX-2 and TNF). Releasing large amounts of antioxidant enzymes.	fermented milk probiotic yogurt	95–101
Antibiotic-associated diarrhea	The most common adverse effect of antimicrobial therapy.	The utilization of antibiotics is considered to disrupt the natural enteric microbiota, causing a reduction in native microorganisms within the gastrointestinal system.	*L. rhamnosus* *L. kefir* *L. gasseri* F71 *L. gasseri* L1 *L. casei* *L. paracassei* *S. thermophilus* *L. acidophilus* *L. plantarum*	Initiate natural killer cell activities. Inhibit pathogen invasion and adhesion. Reinforce intestinal barrier integrity. Enhance phagocytic activities of macrophage.		99–103
HTN	HTN refers to elevated blood pressure levels, posing a significant risk factor for cardiovascular, cerebrovascular and renal diseases worldwide.	Certain gut microbial strains, and an imbalance in gut bacteria known as dysbiosis.	*Lactobacillus helveticus/ Saccharomyces cerevisiae/ Lactobacillus casei* (specifically, *LcS*)	Lowering luminal Ph. Secreting antimicrobial peptides. Inhibition of bacterial invasion. Suppression of bacterial adhesion.	fermented milk products containing specific probiotic strains (LcS)	104–106
Helicobacter pylori eradication	*Helicobacter pylori* is a Gram-negative, flagellated bacteria found in the stomach epithelium, causing severe side effects and disruptions in natural flora.	*Helicobacter pylori* infection leads to adverse effects and changes in stomach flora; STT declines due to complications.	*Lactobacillus/Bacillus subtilis*	Probiotics act as an antidote, inhibiting *Helicobacter pylori* through bacteriostatic and bactericidal effects, reduced cytokines, strengthened gastric defense, and immune interaction.	probiotic supplements (Lactobacillus, *Bacillus subtilis*)	107–110
Autoimmune and inflammatory disorders	Autoimmune diseases result from the immune system targeting the body's own cells, causing inflammation and health issues.	Molecular mimicry, self-antigen modification. Immune reactivity modulation contributes to autoimmune diseases.	Probiotics are used to treat autoimmune conditions such as RA, celiac disease, CD, and more.	Probiotics impact metabolic processes: short-chain fatty acids, tryptophan metabolism, nucleoside signaling, and histamine-2 receptor activation.	Probiotic supplements tailored for autoimmune disease.	111–113
Type 1 diabetes	Type 1 diabetes is an autoimmune disease where the immune system targets pancreatic beta-cells, causing decreased insulin production.	Genetic predispositions and environmental factors contribute to the development of type 1 diabetes. Autoantibodies and insulitis precede β-cell decline.	Probiotic supplementation with strains like *Bifidobacterium longum*, *Bifidobacterium infantis* and *Lactobacillus* spp. shows potential in preventing autoimmune diabetes.	Probiotics reduce pro-inflammatory cytokines (IL-6, IL-1, TNF-α) and increase anti-inflammatory cytokines (TGF-β, IL-10), modulating the immune response.	Oral probiotic compounds containing specified strains can serve as preventive measures, potentially delaying or preventing autoimmune diabetes onset.	114,115
T2DM	Type 2 diabetes is a prevalent epidemic associated with obesity and gut microbiome alterations, leading to significant health and economic challenges.	Obesity, influenced by the gut microbiome, contributes to T2DM development. Altered gut microbiota affects energy extraction, inflammation, and metabolic processes.	*Lactiplantibacillus plantarum/ Bifidobacterium lactis/ Lacticaseibacillus rhamnosus/ Lactobacillus gasseri*, and *Bifidobacterium lactis*	Probiotics enhance gut integrity, reduce systemic lipopolysaccharides, improve insulin sensitivity, regulate glucose, lipids, and immune responses.	Probiotic supplements containing specific strains may aid in managing T2DM by improving gut health, regulating metabolism, and modulating immune responses.	116–119

Table 1. Application of probiotics for therapeutic purposes – cont.

Disease	Definition	Etiology	Probiotic strain	Mechanism of action	Useful product	Ref.
Migraine	Recurrent severe headaches, often triggered by specific foods, accompanied by light and sound sensitivity.	Migraines linked to food triggers and inflammation; elevated IgG levels indicate food hypersensitivity.	Various strains modulating the GBA studied, specific effective strains not mentioned.	Probiotics enhance intestinal barrier function through the GBA, regulating serotonin production in the gut.	Probiotic supplements designed to improve GBA may alleviate migraines by reducing inflammation and regulating serotonin.	120
ASD	Developmental disorders characterized by challenges in social interaction, communication and repetitive behaviors.	Potential link between ASD and dysregulated gut microbiota; microbiota composition may influence ASD symptoms.	Bifidobacterium (*B. longum*, *B. breve*, *B. infantis*, *B. bifidum*)/ Lactobacillus (*L. acidophilus*, *L. helveticus*, *L. rhamnosus*, *L. plantarum*).	Probiotics regulate gut microbiota composition, enhance gut barrier integrity, modulate inflammatory pathways, and influence neurotransmission via the GBA.	Probiotic supplements containing specific strains may aid individuals with ASD by improving gut health and potentially alleviating behavioral abnormalities associated with ASD.	121–123

IBD – inflammatory bowel disease; UC – ulcerative colitis; CD – Crohn's disease; COX2 – cyclooxygenase-2; TNF – tumor necrosis factor; HTN – hypertension; LcS – *Lactobacillus casei* strain Shirota; STT – standard therapy efficacy; RA – rheumatoid arthritis; T2DM – type 2 diabetes; IgG – immunoglobulin G; ASD – autism spectrum disorder; GBA – gut–brain axis.

created to investigate the relationships among dietary functional elements, medications and the intestinal microbiota, certain studies have examined the impact of probiotics, prebiotics and synbiotics on the gut microbiota. For example, Duque et al. utilized the SHIME model and discovered that treatment with probiotics, prebiotics and synbiotics had a positive influence on the gut microbiota and metabolic activity in children with autism spectrum disorder.[129] Likewise, Marzorati et al. examined the effects of MegaSporeBiotic™, an oral probiotic made up of 5 bacillus species, on the activity and composition of gut microbiota using the SHIME model. Their results revealed an elevation in *Akkermansia muciniphila*, bifidobacteria and Firmicutes, alongside a reduction in Lactobacillus and Bacteroidetes during the treatment period.[130] Nevertheless, because there have been only a few studies conducted, additional research is crucial to investigate the practicality and viability of in vitro intestinal microbiota simulation models.

Animal models

Animal models are used to study the interactions between hosts, microbes and potential pathogens in controlled environments. Germ-free animals are particularly useful in these studies. These models also facilitate the retrieval of samples from distinct sections of the GI tract, a task that can be difficult in clinical trials. While mice and rats are commonly employed, alternative models such as *Caenorhabditis elegans*, honey bees, *Ciona robusta*, fruit flies, and greater wax moths have been used to study the interactions between probiotics and pathogens. Researchers have investigated the efficacy of probiotics in mitigating pathogenic conditions in these animal models.[131] For instance, Chen et al. demonstrated that certain Lactobacillus strains mitigated *H. pylori* colonization and associated stomach inflammation.[132] Scalfaro et al. employed *Galleria mellonella* larvae to evaluate the antibacterial effects of *L. rhamnosus* GG and *Clostridium butyricum* MIYAIRI 588 against enteric pathogens. Their results suggested the possible usefulness of *G. mellonella* larvae as an in vivo model, complementing in vitro assays for candidate probiotic prescreening.[133] Despite rapid advancements in genome editing technology leading to the establishment of edited rats and mice, their application in probiotic-related research remains limited. Consequently, further investigations employing diverse animal models are crucial for advancing our understanding in this field.

Human clinical experiments

Although in vitro models and animal experiments offer simplicity, controllable experimental conditions, and lower research costs, establishing reliable evidence about the effects of probiotics on human health depends on human clinical trials. These trials have played a significant role in advancing and commercializing probiotic products. Notably, *E. coli*, comprising various strains, many of which are considered opportunistic pathogens, gained recognition as a probiotic primarily due to pivotal human clinical trials, as seen in the case of *E. coli* Nissle 1917.[134] Researchers, such as Dronkers et al., have conducted comprehensive analyses of probiotic clinical trials. Their findings revealed that *L. rhamnosus* GG and *B. animalis* ssp. lactis BB12 are among the most extensively examined probiotic strains.[135] However, it is important to note that despite numerous clinical trials investigating probiotic benefits in GI diseases, the outcomes can be unstable and occasionally contradictory. This variation can be attributed to several factors, for instance, trial design, group size, participant features, and dosage. Therefore, meticulous consideration of probiotic selection, host population and study design is crucial in the careful planning of human clinical experiments.

Discussion

The contentious role of probiotics in various diseases has been a pivotal focus of research across different disciplines for many decades. In the present review, we evaluated the diverse positive and negative facets associated with the utilization of probiotics in addressing a spectrum of disorders, primarily those pertaining to the GI system. The prevalence of various GI disorders, including IBD, CD and UC, has spurred extensive exploration into pharmaceutical and nutritional interventions, notably probiotics, with the objective of attenuating disease progression and ameliorating associated symptoms. The integration of dietary regimens incorporating these agents has demonstrated promise in enhancing patients' quality of life and facilitating partial clinical remission.[136–138] In the context of probiotics' influence on diverse medical conditions, emerging evidence underscores their potential to modulate respiratory immune responses by establishing a microbial interconnection between the respiratory and GI tracts. Moreover, the advantageous effects of probiotic supplementation have been noted in mitigating the frequency of allergic rhinitis episodes.[67] Additionally, probiotics have demonstrated the capacity to modulate the composition of gut microbiota, thereby ameliorating specific symptoms associated with IBS, such as flatulence, bloating and irregular bowel habits. Despite the existence of numerous pharmaceutical interventions for IBS management, probiotics have emerged as a promising adjunct, potentially regulating immune responses in IBS pathophysiology to foster intestinal homeostasis.[47] Regarding the efficacy of probiotics in addressing AAD, select strains, notably *L. rhamnosus* and *S. boulardii*, administered at a dosage of 50 CFU per day, have exhibited utility across various studies.[55] Although probiotics have recently garnered attention as a prospective intervention for combatting VAP in both adult and pediatric populations, further meticulously designed studies are requisite to ascertain their efficacy in influencing primary clinical endpoints and mortality rates.[94] Concerning NEC in preterm neonates, investigations have indicated that supplementation with Lactobacillus, either alone or in combination with Bifidobacterium, diminishes the incidence of this grave condition.[89] The process of the current review, which emphatically studied GI disorders, encompasses the analysis of 10 articles focused on animal or cell culture studies, alongside 18 articles involving human subjects; among these, 12 included healthy controls, with only 4 involving pediatric patients. Notably, 5 studies encompassed more than 100 patients and 12 involved more than 50 patients. However, the majority of studies were based on relatively small sample sizes, thus limiting definitive evaluations. Furthermore, among the studies assessing patients with active disease, primarily with mild-to-moderate severity scores, improvements in clinical activity scores were observed in 2 out of 3 patients.[42,43] These findings suggest the potential adjunctive use of probiotics in conjunction with conventional treatments. Nevertheless, most studies corroborated the notion that probiotics play a significant role in preventing GI diseases and are associated with improved quality of life in patients. The compiled evidence suggests that probiotics could serve as a viable component in the alleviation and prevention of GI diseases. However, the limited number of trials underscores the necessity for further research to substantiate their therapeutic benefits. Notably, probiotics exhibited efficacy in 3 out of 4 studies compared to no treatment, indicating their potential utility as an additional therapeutic option. Current data suggest the potential utility of probiotics in the prevention of various GI disorders, presenting a promising avenue for novel treatment strategies. While animal studies have contributed valuable insights, they offer a limited scope of understanding. Furthermore, no discernible differences in treatment modalities besides probiotics or sample characteristics were observed between compared groups, highlighting the potential role of probiotics as an adjunctive therapeutic option, particularly when combined with conventional treatment approaches. Notably, most trials enrolled patients with active disease, with only 5 studies examining patients with confirmed inactive disease, yielding positive results in prolonging remission and improving clinical scores in 3 instances. The most important achievement in this field is the application of probiotics in the treatment of COVID-19, which showed a therapeutic effect by regulating the gut–lung axis and mucosal immune system. These findings suggest the promising efficacy of probiotics even when compared to established therapeutic options. Nonetheless, the limited number of studies underscores the imperative for further research to validate this hypothesis.

Limitations

This review is subject to several limitations. It is essential to acknowledge that the process of comparing studies was challenging due to the observed heterogeneity among trials regarding methodologies, including dosages and concurrent treatments administered to patients. Moreover, the majority of studies analyzed samples comprising fewer than 100 patients. While most trials did not reveal significant differences in sample characteristics and treatment options, well-designed, double-blinded, randomized clinical trials are indispensable for fully understanding the role of probiotics in GI diseases. Furthermore, the necessity for a comprehensive meta-analysis to uncover potential variations among research studies can also be regarded as a limitation. The heterogeneity of studies and the requisite sample size are critical factors in interpreting research outcomes in this field.

Conclusions

Although probiotics offer potential as therapeutic agents for treating GI diseases, several challenges may hinder their effective application. A comprehensive understanding of these challenges is essential to optimize the use of probiotics in GI conditions. This review highlights the extensive investigation of probiotics across diverse pediatric and adult GI ailments, revealing promising therapeutic prospects. Probiotics have been demonstrated to have a beneficial impact on a range of health outcomes, including the treatment of functional GI disorders, acute diarrhea and AAD, as well as the prevention of NEC in premature infants. In addition, probiotics have shown efficacy in mitigating colic in infants, reducing school absenteeism in children and potentially influencing allergic conditions, while also providing preventive benefits against infections such as *C. difficile* colitis and VAP, underscoring the versatility of probiotic interventions. Insights from various research methodologies, including in vitro studies, animal models and human clinical trials, contribute significantly to elucidating the mechanisms underlying probiotic interactions with pathogens and host systems. However, the variability in outcomes observed across studies necessitates careful consideration of factors such as probiotic strains, dosage and study design in future research endeavors. Despite these challenges, probiotics have emerged as valuable allies in promoting GI health, with ongoing investigations poised to uncover additional applications and refine their clinical use.

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